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The relationship between sodium glucose co-transporter 2 inhibitors and diabetic ketosis/infection: single center retrospective experiences

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ABSTRACT

Aims: Diabetes is a serious social problem in our country and around the world. Beyond hyperglycemia, it causes common and potentially life-threatening complications in all systems. For this reason, beyond the regulation of blood glucose, a holistic approach and combating complications are important in diabetes management. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a type of antidiabetic medication that effectively regulate blood glucose levels and provide cardiac and renal protection, regardless of the decrease in blood glucose. Despite its strong effectiveness, it is seen as risky in terms of diabetic ketosis and infection, which limits its use. We aimed to investigate the legitimacy of concerns by examining the relationship between SGLT-2 inhibitors and diabetic ketosis or infection.

Methods: Our study was designed single-center and retrospectively. 152 patients over the age of 18 who were treated as inpatients in our clinic with diabetic ketosis between January 2020 and June 2023 were included in the study. In these patients, ketosis and the severity of the infection clinic, if any, were examined through various parameters among type 2 diabetic patients using SGLT-2 inhibitors, type 2 diabetic patients not using SGLT-2 inhibitors, and type 1 diabetes patients. These parameters were determined by the patient's blood and urine biochemistry tests at admission and discharge, the duration of ketosis treatment, the duration of intravenous antibiotic use, and the duration of hospitalization.

Results: Within the scope of the study, type 2 diabetic patients using SGLT-2 inhibitors were compared with type 2 diabetic patients not using SGLT-2 inhibitors and type 1 diabetic patients. In patients using SGLT-2 inhibitors, the leukocyte count in urine, an indicator of urinary tract infection, was found to be significantly higher ($p<0.002$). When the blood biochemistry tests of the patients at the time of admission were compared in terms of ketosis severity, no significant difference was detected between the groups. No significant difference was detected in terms of ketosis treatment duration, intravenous antibiotic use duration, or hospitalization duration.

Conclusion: We believe that we have obtained data showing that ketoacidosis and infection complications associated with SGLT-2 inhibitors are manageable and controllable. Based on this, we recommend that further research be conducted on the side effects of SGLT-2 inhibitors, emphasizing their additional systemic benefits, and that the place of these agents in diabetic treatment should be discussed.

Keywords: Diabetes mellitus, diabetic ketosis, diabetic ketoacidosis, sodium glucose co-transporter 2 inhibitors, infection, antibiotics

INTRODUCTION

Diabetes mellitus (DM), with its increasing momentum in recent years and all the problems it causes, threatens life all over the world and in our country and is seen as a global health crisis.[1,2] In a study, it was predicted that the number of diabetic patients living in the world in 2045 will reach 783.2 million.[3] The situation in our country is not much different from that of other societies. In the TURDEP-2 study conducted in 2011, it was found that the prevalence of DM in our country was 16.5%.[4]

Patients must meet certain criteria to be diagnosed. 1) Plasma fasting glucose level of 126 mg/dl and above after roughly 8 hours of fasting; 2) DM is diagnosed when randomly measured plasma glucose levels are 200 mg/dl or more at any time and symptoms are present; 3) Glycated hemoglobin A1c (HbA1c) levels are 6.5% (48 mmol/L) or more; and 4) plasma glucose levels are 200 mg/dl or more at 2 hours after oral ingestion of 75 grams of glucose solution.[5] DM is categorized under 4 main headings according to the pathophysiology of development: type 1 DM, type 2 DM, gestational diabetes, and other specific types.[6] Among the diabetes types, type 2 DM has the highest prevalence and accounts for approximately 90% of all diabetes cases.[7]

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Metformin is the most commonly used drug as a first-line treatment for DM due to its safety, cost-effectiveness, and cardioprotective properties.8 According to current American Diabetes Association (ADA) guidelines, sodium glucose co-transporter-2 (SGLT-2) inhibitors are recommended as second-line treatment immediately after metformin in patients with atherosclerotic cardiovascular history, heart failure, and chronic kidney disease.[9,10] They act by inhibiting glucose reabsorption from the proximal renal tubules and increasing glucose excretion through the urinary system; these agents, which act through insulin-independent pathways, have many advantages, such as having no risk of hypoglycemia, having diuretic and blood pressure-lowering effects, causing weight loss, and being cardioprotective.

In addition to their advantages, SGLT-2 inhibitors also have side effects related to their mechanism of action. The first of these is that they cause more genitourinary infections than other agents in relation to the glycosuria pathway.[11,12] Another side effect is that they predispose to diabetic ketoacidosis (DKA) with increased lipolysis and free fatty acid formation in adipose tissue and increased ketone body formation in plasma after a series of reactions.[13-15]

METHODS

Ethics

For this specialty thesis study, permission was obtained from the Kırıkkale University Non-interventional Researches Ethics Committee with decision number 2023.09.07 on 06.09.2023. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

In this retrospective cross-sectional study, 152 patients over the age of 18 who were hospitalized with a diagnosis of diabetic ketosis or ketoacidosis between January 2020 and June 2023 at Kırıkkale University Faculty of Medicine Hospital were identified and included in the study by scanning through the hospital information management system.

Patients who did not meet the criteria for diabetic ketoacidosis and ketosis at the time of hospitalization, those who subsequently developed diabetic ketoacidosis or ketosis while being followed up in the hospital for any other reason, patients younger than 18 years of age, and patients with incomplete clinical and laboratory records were not included in the study.

Some clinical parameters were defined to evaluate the clinical severity and course of the patients.

- **Ketosis treatment duration:** It includes the time between the start and end of the treatment of diabetic ketoacidosis, or ketosis, in our clinic.
- **Duration of intravenous antibiotics:** It is calculated for patients who received antibiotics and indicates how many days intravenous antibiotics were administered.
- **Length of hospitalization:** The number of days the patient was hospitalized. It is calculated to include the day the patient was hospitalized and the day the patient was discharged.

The first blood and urine tests of the patients included in the study were analyzed at admission. These tests included urea, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, magnesium, phosphorus, calcium, and albumin in the blood; pH, CO_2, HCO_3, lactate in venous blood gas; a hemogram includes leukocytes (white blood cells; WBC), hemoglobin (Hgb), platelets (Plt), neutrophils, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Glucose, ketone, density, and leukocyte values in urinalysis were included in the study.

Statistical Analysis

The categorical variables in the study were presented as frequency (n) and percentage (%) and analyzed by Pearson Chi-square and Fisher's exact test. The Shapiro-Wilk test determined whether the data adhered to a normal distribution. In the analysis of the difference between the continuous variables of two independent groups, the Mann-Whitney U test was used when the data did not conform to the normal distribution, and an independent t-test was used when the data did conform to the normal distribution. Data analysis was performed with the IBM SPSS 23.0 package program (IBM Corp., Armonk, NY). p values less than 0.05 were considered statistically significant.

RESULTS

Of the 152 patients included in the study, 38 had type 1 DM and were defined as type 1 (group 1). The medication use of 114 type 2 DM patients was analyzed, and 42 patients using SGLT-2 inhibitors were divided into a group called SGLT-2 inhibitors (group 2), and the remaining 72 patients not using SGLT-2 inhibitors were divided into another group called non-SGLT-2 inhibitors (group 3).

Gender, whether the patients were followed up in the intensive care unit or not, and the DK/DKA during hospitalization were analyzed for each group; 22 (57.9%) in the type-1 group, 29 (29%) in the SGLT-2 inhibitors group, and 39 (54.2%) in the non-SGLT-2 inhibitors group were female. The rate of patients requiring intensive care unit follow-up was 23.7% (9 patients) in type-1, 27.6% (5 patients) in SGLT-2 inhibitors, and 8.3% (6 patients) in non-SGLT-2 inhibitors. The DKA rate was 42.1% in the type-1 group, 16.7% in the SGLT-2 inhibitors group, and 15.3% in the non-SGLT-2 inhibitors group.

Age, number of days of hospitalization, duration of IV antibiotic use, duration of ketosis treatment, and history of DM were analyzed. The disease duration was considered to be 0 years for patients diagnosed at admission. The mean ages, duration of hospitalization, rates and duration of IV antibiotic treatment, duration of IV antibiotic treatment, and duration of diabetes for the type-1, non-SGLT-2 inhibitors group, and SGLT-2 inhibitors group are given in Table 1.

The mean, standard deviation, minimum and maximum values were determined by analyzing the last blood biochemistry tests of the patients at admission and before discharge within the groups (Table 2).

There was no significant difference between patients with and without SGLT-2 inhibitors in terms of IV antibiotic initiation rate, initial CRP, ESR, WBC, PLT, neutrophil, and TIT nitrate values. In contrast, there was a significant difference between the two groups in terms of urine leukocyte values at admission ($U=1122.50$; $p<.05$). In particular, when the arithmetic mean of both groups was analyzed, it was observed that the urine leukocytes at admission of patients who used SGLT-2 inhibitors (M=1.02) were higher than those who did not use SGLT-2 inhibitors (M=.50).

Table 1. Rates and duration of initiation of IV antibiotic treatment in patients with ketosis and ketoacidosis; duration of diabetes

	Type-1			Non-SGLT-2 inhibitors			SGLT-2 inhibitors		
	Mean	SD	Min-Max	Mean	SD	Min-Max	Mean	SD	Min-Max
Age[1]	31.82	11	19-55	52.07	14.88	18-86	61.50	12.78	35-81
Days of hospitalization[1]	6.13	3.03	2-17	7.28	6.67	2-36	5.38	2.90	1-14
AB* usage[2]		28.94 (%)			34.72 (%)			47.71 (%)	
IV AB* duration[1] (days)	7.73	5.04	2-20	9.04	5,51	2-20	6.07	2.97	1-10
Ketosis treatment duration[1] (hours)	28.00	32.39	1-168	23.60	26.54	2-168	31.24	34.66	3-173
Disease duration[1] (years)	9.50	7.73	0-30	8.22	8.40	0-28	14.63	8.02	1-30

1 Except for the antibiotic use parameter, parameters are expressed as Mean (Mean), Standard deviation (SD), Minimum value (Min), Maximum value (Max). 2 Intravenous antibiotic use parameter is expressed as a percentage (%) only. *AB: Antibiotic

Table 2. The laboratory parameters of the patients at admission and before discharge

	Type-1			Non-SGLT-2 inhibitors			SGLT-2 inhibitors		
	Mean	SD	Min-Max	Mean	SD	Min-Max	Mean	SD	Min-Max
sGlucose	398.61 160.35	162.90 60.43	191-821 72-342	355.47 171.43	105.07 75.29	149-705 80-472	322.31 154.64	135.78 55.87	97-652 59-283
Urea	37.18 26.89	27.04 19.44	11-134 12-123	36.32 28.97	21.50 14.76	10-164 11-95	39.71 31.15	21.30 15.65	12-117 12-92
sCrea	0.98 0.74	0.48 0.31	0.6-2.67 0.4-2.27	0.90 0.75	0.31 0.27	0.19-1.9 0.32-1.63	0.92 0.73	0.35 0.21	0.52-2.35 0.43-1.5
GFR	97.57 113.93	32.76 30.35	23-141 5.5-179	88.04 101.43	26.63 29.94	37-163 34-219	76.48 91.43	26.55 20.45	11-116 44-148
ALT2	17.19	10.73	6-58	21.68	14.83	5-74	15.80	7.45	4-38
AST2	18.68	7.46	9-42	22.36	15.17	8-106	17.37	6.85	4-35
Sodium	132.95 137.34	4.88 3.21	118-140 130-147	135.00 138.22	5.01 3.02	122-157 131-147	135.98 138.54	3.95 3.35	127-144 131-148
Potassium	4.72 4.23	0.72 0.46	3.9-7.86 3.19-5.27	4.55 4.20	0.71 0.47	2.6-6.6 3.2-5.2	4.54 4.36	0.67 0.48	3.5-5.9 3.3-5.4
Calcium	9.35 9.22	0.67 0.45	7.2-11,3 8.4-10.1	9.38 9.18	0.66 0.73	7.8-10.9 7.4-10.8	9.59 9.37	0.76 0.63	7.9-11.3 8.3-10.9
Phosphorus	3.38 3.93	1.16 1.06	1-6.1 1.24-5.9	3.23 3.76	1.24 0.87	1.1-9.2 0.9-5.9	3.74 3.66	0.79 0.78	2.2-5.6 1.5-5.2
Albumin	4.38 3.94	0.53 0.47	3.6-5.6 2.9-4.9	4.07 3.77	0.55 0.51	2.6-5.2 2,8-5.1	4.18 3.91	0.57 0.57	2.5-5 1.9-4.7
Magnesium	1.96 1.97	0.25 0.29	1-2.4 1.3-2.8	1.98 1.95	0.34 0.26	1-3.4 1.3-2.5	2.02 1.93	0.28 0.25	1.5-2.84 1.4-2.6
CRP2	28.86	56.49	0.1-239	59.22	96.01	0-380	36.88	60.25	0-237

[1]Mean: Mean, SD: Standard Deviation, Min-Max: Refers to Minimum and Maximum Values.
[2]Only ALT, AST and CRP statistics are generated from and represent the values at the time of application. All parameters, with the exception of these three parameters, are calculated from the values at admission in the first (top) row of the block and from the last values before discharge in the second (bottom) row and represent these measurements.
[3]The units of the defined parameters are as follows: sGlucose: Serum glucose: mg/dl, Urea: mg/dl, sCrea: Serum creatinine, mg/dl, GFR: Glomerular filtration rate, ml/min/1.73m2 (CKD-EPI), Alanine aminotransferase: ALT: U/L, AST U/L, Sodium: mmol/L, Potassium: mmol/L, Calcium: mg/dl, Phosphorus: mg/dl, Albumin: g/dl, Magnesium: mg/dl, CRP: mg/L

There was no significant difference between the duration of ketosis treatment, days of inpatient stay, and days of IV antibiotics in participants who used SGLT-2 inhibitors and participants who did not use SGLT-2 inhibitors ($p>.05$). In other words, the hypothesis that patients on SGLT-2 inhibitors have a more persistent ketosis clinic and require longer treatment than patients following other treatment regimens is rejected.

Venous blood gas pH, CO_2, HCO_3, lactate; urine ketone, glucose, and density were analyzed to examine whether the ketosis clinic was worse at presentation in patients using SGLT-2 inhibitors. No significant difference was found between patients using SGLT-2 inhibitors (group 3) and patients not using SGLT-2 inhibitors (group 2).

DISCUSSION

Although diabetes occurs in all age groups in society, the elderly are more affected by diabetes and its complications. In our study, in a similar way to society, patients with type 2 DM had a higher average age, additional diseases, and chronic complications. It is important to protect these patients from cardiovascular and renal complications and not to confront them with infection or DK/DKA. With this study, we believe we have made meaningful findings about the adverse effects of SGLT-2 inhibitors on patients with diabetes.

There was no difference between the groups in terms of CRP, ESR, WBC, and neutrophils on admission; however, we found a significant difference between the leukocyte values in urine ($U=1122.50$; $p<.05$). This data was in line with the existing opinions. In our study, 58.8% of patients who used SGLT-2 inhibitors were started on IV antibiotics, whereas this rate was 35.3% in patients who did not use SGLT-2 inhibitors. There was no statistically significant difference between these rates. The mean duration of IV antibiotic use was 6.07 days in SGLT-2 inhibitor users and 9.04 days in non-SGLT-2 inhibitor users. The duration of IV antibiotic use in patients using SGLT-2 inhibitors was not significant compared to the others.

Uitrakul et al.[16] reported that patients using SGLT-2 inhibitors had an increased risk of urinary tract infections. In a study examining SGLT-2 inhibitors against DPP-4 inhibitor drugs, it was reported that SGLT-2 inhibitors caused a risk in terms of genital infections, but no difference was found in terms of urinary tract infections.[17] Obviously, considering that SGLT-2 inhibitors act by causing glycosuria, it is not difficult to predict that they may pose a risk for infection in any part of the urinary tract.[18]

In a study conducted by Jeon et al.[19] examining DKA cases in terms of SGLT-2 inhibitors, it was found to be the precipitating cause of infection in 3 (20%) of 15 patients using SGLT-2 inhibitors and 131 (26%) of 508 patients not using SGLT-2 inhibitors and was not statistically significant ($p=0.77$).

Despite the high percentage of antibiotic use, the fact that the mean duration of antibiotic use in patients using SGLT-2 inhibitors was less than 1 week and did not differ statistically against other treatment regimens led us to think that these infections were easy to manage and uncomplicated cases. On the other hand, as a limitation of our study and as an opposing view, it should be noted that while our cases were discharged in a week, cases with a highly complicated course may be followed up with gangrene or abscess in surgical clinics a few steps away from our clinic, and we may be unaware of this situation. Therefore, we think there is a need for long-term and more comprehensive studies on this subject.

SGLT-2 inhibitors have always been blamed for DKA, and there are well-defined theories for how DKA occurs in patients.[20] Liu et al.[21] pointed out that SGLT-2 inhibitor use may increase the risk of DKA. Hamblin et al.[22] found data showing that the risk of developing DKA in inpatients increased with SGLT-2 inhibitor use ($p<0.0001$). On the other hand, a systematic review published by Yang et al.[23] concluded that SGLT-2 inhibitor use did not lead to an increased risk of DKA. Our study is not suitable to contribute to this controversial literature by design. However, we can put this controversy aside and reveal whether SGLT-2 inhibitor treatment is an additional burden to patients by examining the duration of ketosis treatment and hospitalization.

DK/DKA treatment lasted an average of 31.24 hours in patients on SGLT-2 inhibitors and 23.59 hours in type 2 DM patients not on SGLT-2 inhibitors. In type 1 DM patients, this time was 28 hours, noting the higher presence of DKA. Despite the significant difference between the averages, we found that the use of SGLT-2 inhibitors did not cause a statistically significant difference in type 2 DM patients. This lack of differentiation continued in terms of the length of hospitalization. The duration of hospitalization was 7.27 days in patients who did not use SGLT-2 inhibitors, but 5.38 days in those who did. These data were statistically insignificant.

In a study in which patients with type 2 DM and DKA were analyzed separately according to SGLT-2 inhibitor use, the results were similar to our data. In this study, a total of 55 cases, 17 of which used SGLT-2 inhibitors, were retrospectively analyzed. The duration of DKA treatment was 23 hours in SGLT-2 inhibitor users and 20.8 hours in nonusers and was not statistically significant (p .544).[24]

Based on these statistics, we would like to think that DKA and other clinical conditions associated with the use of SGLT-2 inhibitors have roughly no impact on the time patients have to spend in the hospital and do not impose an additional burden on patients and hospitals.

Apart from these parameters, we aimed to obtain information about the severity of the patients' clinical conditions at the time of admission by examining some laboratory parameters at the time of admission. No difference was observed between the patient groups in terms of pH, CO_2, HCO_3, lactate values in venous blood gas, ketone, glucose, and density values in urine. When we reviewed the literature, we found that there were studies supporting our findings. If we compare it with the study conducted by Jeon et al.[19] mentioned above; the mean pH was 7.17, HCO_3 was 8.4 mmol/L, and CO_2 was 20 mgHg in the venous blood gas at admission in patients using SGLT-2 inhibitors. In patients followed up with other treatment regimens, these values were 7.19, 4.8 mmol/L, and 14 mmHg, respectively, and were not statistically different. Although statistical insignificance is common, it is noteworthy that these figures are quite different from our data. Unlike the aforementioned study, in our study, in addition to DKA cases, there were also cases of diabetic ketosis without acidosis, so it is expected that the averages would be much different. Therefore, when comparing these studies, it would be a more accurate approach to examine the statistical difference, not the numbers.

In a two-year retrospective study by Papanastasiou1 et al.[25] cases of DKA directly related to SGLT-2 inhibitors were analyzed against cases of DKA due to other causes, and they reached important data in our opinion. This study reported no difference in the severity of DKA between the two groups based on the levels of venous blood gas samples. However, there was a statistical difference in the resolution of DKA, or, in other words, the duration of DKA treatment, against SGLT-2 inhibitors (39 hours versus 19 hours, $p<0.001$). In addition, the duration of hospitalization also showed a result against SGLT-2 inhibitors (11 days versus 5.5 days).

Compared to our study, despite the similarity in blood picture, this difference in treatment and discharge times led us to think about this study, and we think we have found an explanation for this difference. In the aforementioned study, it was noted that more intravenous fluids were used in the treatment of the SGLT-2 inhibitor group (14L vs. 5.5L, $p=0.013$) and in our study, to remind you again, there were not only DKA cases but also DC cases. We know that SGLT-2 inhibitors cause glycosuria and fluid loss, and we know the importance of fluid in the development and resolution of DKA. According to our hypothesis, we treated not only severely dehydrated DKA cases but also relatively less dehydrated and early diabetic ketosis cases, and these early cases were easily treated, causing the statistical difference between the studies.

There is a national cohort study on DKA in Korea.[26] In this study, SGLT-2 inhibitors versus DPP-4 inhibitors were examined in terms of DKA. It was reported that there was no difference in the risk of hospitalization for DKA between the two groups, but the risk was increased in patients with microvascular complications of diabetes or those taking diuretics.

Based on these data, we may think that SGLT-2 inhibitors increase the risk of complications for patients with fluid balance problems and that the DKA clinics that will develop in these patients will be persistent and more dangerous. If this is correct, the main idea to be drawn from this is that the same importance given to the renal function and HBA1c of the patients when deciding to use SGLT-2 inhibitors should also be given to the evaluation of the fluid volume of the patients. Only in this way can we offer the right patients additional cardiac and renal protection through SGLT-2 inhibitors without putting them at risk, and at-risk patients can be easily identified and protected from DKA caused by these agents.

CONCLUSION

Based on the available evidence, we think the following question needs to be asked: Are we forcing patients to live in the hospital and suffer the pain of infection while desiring potential benefits, or are we withholding a drug that promises cardiac and renal protection from patients for nothing?

Considering the mechanism of action of these agents, it can be easily predicted that they may pose a risk in terms of

infection and ketosis. Indeed, many studies in the literature have drawn attention to these risks and presented strong data; however, as in our study and many similar studies, there are also data in the literature showing that the risks of SGLT-2 inhibitors are not different from others. According to our analysis, the management of these SGLT-2 inhibitor-related complications is not more challenging and does not produce worse hospital outcomes. In addition to this, we consider SGLT-2 inhibitors to be an important family of drugs for DM management with additional systemic benefits. There is a need to define parameters that can predict complications associated with the use of SGLT-2 inhibitors and to determine the importance of risk factors in order to prescribe these agents correctly to the right patients in the clinic. For the holistic management and healthier lives of diabetic patients, we believe that comprehensive and long-term research on SGLT-2 inhibitors is essential to resolving the uncertainties about this family of drugs.

ETHICAL DECLARATIONS

Ethics Committee Approval

This thesis study was initiated with the approval of the Kırıkkale University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 06.09.2023, Decision No: 2023.09.07).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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